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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/808,827	02/28/97	GLINZBURG	03F97 01A

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EXAMINER
BRUSCA, J

ART UNIT	PAPER NUMBER
1631	30

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	08/808,827	GUNZBURG ET AL.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,7,9-26,28,29,31 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,7,9-26,28,29,31 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 23 April 2001 has been entered.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 5, 7, 9-26, 28, 29, 31, and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims have been amended to recite the phrase "a heterologous promoter which is not derived from the retrovirus or a related retrovirus upon which the retroviral vector is based." The applicants have failed to note support for the amendment as required in MPEP 714.02 and 2163.06. A review of the specification does not reveal subject matter that supports the amendment recited above. While the specification provides an example of insertion of a promoters from a cellular gene, it does not provide support for the genus of promoters that are

not derived from a retroviral vector, or for the genus of promoters that are not from a retrovirus that is related to the retroviral vector.

4. The rejection of claims 7, 20, and 21 under 35 U.S.C. 112, second paragraph, in the Office action mailed 18 April 2000 is withdrawn in view of the amendment received 23 April 2001.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 5, 7, 9-26, 28, 29, 31, and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5, 7, 9-26, 28, 29, 31, and 32 are indefinite for recitation of the phrase "a heterologous promoter which is not derived from the retrovirus or a related retrovirus upon which the retroviral vector is based" because the metes and bounds of the claimed promoter are unclear.

Claim 7 is indefinite because it is limited in the preamble to a vector comprising a promoter, but the promoter is selected from a group that includes promoters and regulatory elements, rather than a group of promoters.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al.

Couture et al. (Reference AS in the Form PTO-1449 filed 9/23/97) shows retroviral vectors comprising a substitution of a portion of the 3' U3 region with the corresponding region of 5 different murine retroviruses, including leukemia and sarcoma retroviruses. Couture et al. shows on page 669 column 2 that the first 40 nucleotides of the original vector are retained in the substitution of the U3 region. The vector of Couture comprises a chloramphenicol acetyl transferase marker gene and a neomycin resistance gene, which are considered to be cellular sequences. Couture et al. shows in the abstract that after packaging, the substituted U3 region appears at the 5' LTR and serves as a promoter for all genes in the body of the vector, and that different LTR constructs were preferentially expressed in specific cell types. Couture et al. states

in the second paragraph of the Results section on page 669 that U3 regions are bound by cellular factors. Couture et al. shows in Table 3 that their chimeric LTR promoters are active in a cell type specific manner. Couture et al. state on page 670 that promoter suppression or interference may occur within retroviral vectors containing internal promoter elements. Couture et al. states on page 667 that retroviral vectors with target cell specificity have utility in gene therapy protocols. Couture et al. shows the use of packaging cell lines PA317 and GP&E86 on page 669 to package their retroviral vectors. Couture et al. does not show a vector comprising a multiple cloning site in the U3 region.

Faustinella et al. shows in figure 1 Moloney murine leukemia retroviral vector pS3. pS3 comprises a partial deletion of the 3' U3 region, into which has been inserted a polylinker with unique cloning sites, for example the Bsa AI site and the Nae I site used to construct the vectors of figure 2.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vectors of Couture et al. by adding the multiple cloning site of Faustinella et al. because Faustinella et al. shows that multiple cloning sites may be used to insert sequences of choice in a U3 region of a retroviral vector.

9. Claims 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above, and further as evidenced by Miller et al. and Panganiban et al.

Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above do not explicitly show an altered retroviral gene or a partially deleted sequence involved in integration of retroviruses.

Couture et al. shows in figure 1 a retroviral vector LCSN and a derivative of LCSN. Couture et al. shows in the Methods section on page 668 that their vectors are derivatives of the vectors of Miller et al.

Miller et al. shows in figure 2 that their vectors retain the phi+ packaging sequence, but lack the gag, pol, and env genes of a replication-competent retrovirus.

Panganiban '84 shows that the 3' end of the pol gene encodes the int locus that is required for integration of the reverse transcribed retroviral genome to form a provirus.

Therefore the vectors of claims 13 and 14 are taught by Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above, and further as evidenced by Miller et al. and Panganiban et al.

10. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above, and further in view of Price et al.

Claim 10 is drawn to the vector of claim 1 further limited to a vector derived from a BAG vector.

Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above does not show a vector derived from a BAG vector.

Price et al. shows a BAG retroviral vector comprising a beta galactosidase reporter gene, and that the vector can be used to identify cells and progeny of cells infected with the vector.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above by basing the construction on

a BAG vector of Price et al. because Price et al shows that a vector with a beta-galactosidase reporter gene may be used to identify cells and progeny of cells infected with the vector.

11. Claims 15, 20, 21, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above, and further in view of Longmore et al. and Kay et al.

Claim 15 is drawn to the vector of claim 1 comprising a DNA fragment homologous to a cellular sequence. Claim 20 is drawn to a method of introducing nucleotide sequences by infection with the retroviral vector of claim 17 in humans or animals or cultured cells of humans or animals. Claim 21 is drawn to the method of claim 20 further limited to comprise genes, regulatory sequences, or promoters. Claim 26 is drawn to a pharmaceutical comprising the retrovirus of claim 22.

Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above does not show use of retroviral vectors in an animal.

Longmore et al show in the abstract that mice infected with a retroviral vector expressing the erythropoietin receptor had increased platelet counts and splenic megakaryocytes.

Kay et al. shows in the abstract and throughout that hemophiliac dogs infected with a retroviral vector expressing factor IX shows improved levels of clotting and thromboplastin times for greater than 5 months after treatment.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above to express a therapeutic protein because both Kay et al. and Longmore et al. show that retroviral vectors may be used to

express therapeutically effective levels of a recombinant protein in an animal. Regarding the limitation in claim 15 to a vector comprising a DNA fragment homologous to a cellular sequence, the erythropoietin receptor gene of Longmore et al. or the factor IX gene of Kay et al. teach such a sequence in a retroviral vector.

12. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above, and further in view of Mee et al.

Claim 7 is drawn to the vector of claim 5 further limited to a target sell specific regulatory element and promoter selected from the group consisting of Whey Acidic Protein specific regulatory elements and promoters, Mouse Mammary Tumor Virus specific regulatory elements and promoters, beta lactoglobulin and casein specific regulatory elements and promoters, pancreas specific regulatory elements and promoters, lymphocyte specific regulatory elements and promoters, and mouse mammary tumor virus specific regulatory elements and promoters conferring responsiveness to glucocorticoid hormones or directing expression to the mammary gland.

Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above does not show the claimed promoter or regulatory elements.

Mee et al. shows a retroviral vector comprising a mouse mammary tumor virus LTR, and that the LTR expressed a gene after induction with dexamethasone. Mee et al. state on page 292 that their vector is a potentially powerful tool for the manipulation of gene expression in a variety of cell types.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. by insertion of a promoter region in a deleted 3' U3 region of a retroviral vector results in the expression of vector genes under the control of the inserted promoter in a cell type specific manner because Mee et al. show that their LTR promoter may be used to manipulate gene expression in a variety of cell types.

13. Applicant's arguments filed 23 April 2001 have been fully considered but they are not persuasive.

The applicants state that the cited references teach away from the use of heterologous promoters in retroviral vectors, however Couture et al. states in the introduction on page 668: "Substitution of various exogenous retroviral LTR transcriptional control elements (U3) into the backbone of currently available MoMLV-based vectors should yield a set of comparable vectors with a range of tropism and expression levels."

The applicants state that Junker et al, provided in the amendment received 10 May 1999, shows that insertion of heterologous promoters results in rearrangements and unstable vectors, and teaches away from use of heterologous promoters inserted in the LTR of a retroviral vector. However, Junker et al. concludes on page 643 that the rearrangements observed are due to the presence of short direct 22 base repeats that flank the insertion within each LTR in the vector used by Junker et al. Therefore, Junker et al. shows that direct repeats within an LTR can result in instability, but does not show that large scale repeats such as the LTR normally present in retroviruses or the inserted LTR of Couture et al. would lead to instability.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca, Ph.D. whose telephone number is (703) 308-4231. The examiner can normally be reached on Monday -Friday 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward can be reached on (703) 308-4028. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-5137 for regular communications and (703) 746-5137 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

John S. Brusca, Ph.D.
Primary Examiner
Art Unit 1631

jsb
July 12, 2001